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Safety-Net Versus Private Hospital Setting for Brain Metastasis Patients Treated With Radiosurgery Alone: Disparities in Follow-Up Care and Outcomes

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Abstract

Background: Stereotactic radiosurgery (SRS) alone is an increasingly accepted treatment for brain metastases, but requires adherence to frequently scheduled follow-up neuroimaging due to risk of distant brain metastasis. The effect of disparities in access to follow-up care on outcomes after SRS alone is unknown.

Methods: This retrospective study included 153 brain metastasis patients treated consecutively with SRS alone from 2010 through 2016 at an academic medical center and a safety net hospital located in Los Angeles, California. Outcomes included neurologic symptoms, hospitalization, steroid use and dependency, salvage SRS, salvage whole brain radiotherapy (WBRT), salvage neurosurgery, and overall survival (OS).

Results: Of 153 patients, 93 were private hospital patients and 60 were safety net hospital patients. Median follow-up time was 7.7 months. Safety net hospital patients received fewer follow-up neuroimaging studies (1.5 safety net, 3 private; p=0.008). In multivariable analysis, safety net hospital setting was a significant risk factor for salvage neurosurgery (HR 13.65, p<0.001), neurologic symptoms (HR 3.74, p=0.002), and hospitalization due to brain metastases (HR 6.25, p<0.001). More clinical visits were protective for hospitalization due to brain metastases (HR 0.75, p=0.002) while more neuroimaging studies were protective for death (HR 0.65, p<0.001).

Conclusions: Safety net hospital patients with brain metastases treated with SRS alone had fewer follow-up neuroimaging studies and higher risk of neurologic symptoms, hospitalization for brain metastases, and salvage neurosurgery compared to private hospital patients. Clinicians should consider practice setting and patient access to follow-up care when deciding on the optimal strategy for treatment of brain metastases.

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Glossary

ACS; American Community Survey

AJCC; American Joint Committee on Cancer

CI; Confidence interval

CTCAE; Common Terminology Criteria for Adverse Events

GPA; Graded Prognostic Assessment

Gy; Gray

HR; Hazard ratio

IQR; Interquartile range

KPS; Karnofsky Performance Scale

LAC+USC; Los Angeles County + USC Medical Center

MRI; Magnetic resonance imaging

NCCN; National Comprehensive Cancer Network

OS; Overall survival

PACS; Picture archiving and communication system

PH; Private hospital

RCT; Randomized controlled trial

SNH; Safety net hospital

SRS; Stereotactic radiosurgery

USC; University of Southern California

WBRT; Whole brain radiation therapy

Introduction

The standard of care for treatment of brain metastases has historically been whole brain radiation therapy (WBRT) with surgery or stereotactic radiosurgery (SRS) as adjuvant treatment.[1] However, with improving systemic therapies and survival in patients with metastatic disease, there has been growing interest in treatment strategies that offer high quality of life and prolonged intracranial control.[2] Recently, SRS alone has become an increasingly accepted treatment option due to improved neurocognitive preservation compared to patients treated with SRS and WBRT demonstrated in two randomized controlled trials (RCTs).[3,4] SRS delivers a single, high dose of focal radiation to the tumor while sparing adjacent normal brain tissue and is administered in a single session. Multiple RCTs have shown no improvement in overall survival with the addition of WBRT to SRS.[5,6] The success of SRS alone, however, depends on close clinical observation with neuroimaging due to the increased risk of distant brain metastasis failure associated with the omission of WBRT.[4–6]

Unfortunately, not all patients have equal access to recommended follow-up clinical care, neuroimaging, and salvage treatment. Disparities in cancer outcomes and access to cancer care among different racial and socioeconomic groups are well recognized in the medical literature.[7–14] Patients with melanoma who have Medicaid or are uninsured are more likely to present with advanced disease, less likely to receive treatment, and have worse overall survival.[7] Black patients have worse outcomes and survival in advanced breast cancer even after adjusting for confounding factors.[8] Black and Hispanic patients are less likely to receive radiation therapy for locally advanced breast cancer.[9] Increasing distance to the nearest urologist is associated with an increased chance of being diagnosed with high risk prostate cancer, but disproportionately affects black patients.[14]

The effect of disparities in access to care on patient outcomes when utilizing a strategy of treating brain metastases with SRS alone, however, is unknown. As SRS becomes more widely utilized in diverse clinical settings and patient populations, the potential impact of demographics and access to care on patient outcomes will continue to grow, as will the importance of understanding these factors.[2] Thus, in the present study, we compared clinical outcomes between safety net hospital (SNH) and private hospital (PH) patients treated with SRS alone to test the hypothesis that, due to worse neurologic outcomes, SRS alone with observation may not always

be suitable for patients originating from a SNH environment who may have barriers to appropriate follow-up care.

Methods

Study Population

This retrospective cohort study was approved by the University of Southern California (USC) Keck School of Medicine Institutional Review Board. We included patients who received initial SRS for treatment of brain metastases at USC Norris Comprehensive Cancer Center (Norris, PH) or Los Angeles County + USC Medical Center (LAC+USC, SNH) from 2010-2016 using institutional treatment databases.

Setting and Patient Flow

Both LAC+USC and Norris are USC teaching hospitals, but each hospital has a separate administration. LAC+USC is the largest safety net hospital in Los Angeles County, with the designation of "safety net" meaning that it is legally obligated to provide medical care for patients regardless of their insurance status or ability to pay for services. Patients in our study from both hospitals were presented at the same multi-disciplinary tumor board consisting of neurosurgeons, radiation oncologists, and neuroradiologists, and were deemed to be candidates for SRS based on their clinical history and neuroimaging.

LAC+USC patients were initially evaluated and determined to be candidates for SRS by the LAC+USC team. They were presented at the tumor board and referred to Norris for consultation with the SRS treatment team. The SRS procedure was performed at Keck Hospital of USC (Keck). After the SRS procedure, LAC+USC patients returned to LAC+USC for follow-up care.

Norris patients were initially evaluated at Norris and determined to be candidates for SRS by the Norris team. They were presented at the same tumor board, treated with SRS at Keck, and then continued their follow-up care at Norris. The recommended routine follow-up interval for clinical and neuroimaging visits after SRS was every 2 - 3 months at Norris and LAC+USC, consistent with National Comprehensive Cancer Network (NCCN) guidelines.[15]

Radiation Delivery

All patients were treated with single-fraction Gamma Knife radiosurgery using Gamma Knife Perfexion (Elekta AB, Stockholm, Sweden). Patients were immobilized with a stereotactic head frame. The frame was affixed to the cranium of the patient while under conscious sedation. Magnetic resonance imaging (MRI) of the brain was performed for treatment planning and radiation therapy was delivered the same day. No planning target volume margins were added for any patients treated as all patients included in the study had intact brain metastases.

Data Source and Approach

Medical records were reviewed to obtain patient demographic information including age, race, sex, insurance status, and residential zip code. Household incomes were based on aggregate zip code data from the American Community Survey (ACS) 2014. All cancer staging was performed with the American Joint Committee on Cancer (AJCC) 7th edition guidelines.[16] Tumor volumes and maximum diameters were obtained from radiation treatment planning software or measured manually in the institutional picture archiving and communication system (PACS). The number of clinical visits and neuroimaging studies included only those performed as part of routine follow-up. Neurologic symptoms were identified from medical records and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Only neurologic symptoms attributable to brain metastases were included in analysis. Severe neurologic symptoms were defined as grade ≥3. Date of last follow-up was the last clinical encounter documented in medical records. Survival data was obtained from institutional cancer registries and public online databases.

Statistical Analysis

Baseline patient information, treatment characteristics, number of clinical follow-ups, number of neuroimaging follow-ups, steroid use and dependency, and rates of salvage treatments were compared with the Wilcoxon rank sum test and Pearson chi-square test. Development of new neurologic symptoms, hospitalizations, salvage surgery, salvage SRS, salvage WBRT, and overall survival (OS) were analyzed as time-dependent variables with the Kaplan-Meier method with time calculated from the date of first radiation treatment to the event and censoring

occurring either at death or date of last follow-up. Statistical significance comparisons between the two hospitals were calculated using the log-rank test.

Univariate and multivariate analysis were performed with the Cox proportional hazards model. All risk factors, including institution, age, race, income, education, tumor histology, stage at diagnosis, time from brain metastasis diagnosis to SRS, clinical visits, neuroimaging studies, KPS, GPA, neurologic status at baseline, number of brain metastases, and total tumor volume were entered into univariate analysis with each clinical outcome. Risk factors with $p<0.10$ and other clinically relevant variables were further entered into multivariable analysis. Significance was considered $p<0.05$. All analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC) and R software (version 3; R Foundation, Vienna, Austria).

Results

176 patients received SRS consecutively for brain metastases from 2010-2016, including 110 PH and 66 SNH patients. 6 PH (5%) and 6 SNH (9%) patients were excluded due to prior WBRT. 1 PH (0.9%) patient was excluded due to treatment with upfront SRS + WBRT, and 10 PH (9%) patients were excluded due to lack follow-up after SRS treatment. In total, 153 patients were analyzed, including 93 PH (85%) and 60 SNH (91%) patients.

Patient and Treatment Characteristics

The median age was 59 years (IQR 50-66), 78 (51%) patients were female, and 65 (42%) patients were white non-Hispanic (**Table 1**). SNH patients were significantly younger (median 56 years SNH; 61 years PH; $p=0.001$), had lower median household income ($48,754 SNH; $72,192 PH; $p<0.001$), and had lower median high school graduation rate (69.8% SNH; 88.7% PH; $p<0.001$). Of the SNH patients, 11 (18%) patients were white non-Hispanic and 32 (53%) were Hispanic whereas of the PH patients, 54 (58%) were white non-Hispanic and 15 (16%) were Hispanic ($p<0.001$). In addition, more SNH patients had late stage (III-IV) at diagnosis of cancer (91% SNH; 78% PH; $p=0.04$), and SNH patients had longer median time from diagnosis of brain metastases to SRS treatment (43 days SNH; 22 days PH; $p<0.001$). There was no significant difference between the groups in terms of KPS, graded prognostic assessment (GPA), baseline neurologic status, tumor histology or mutation status, prior chemotherapy or

neurosurgery, number of brain metastases treated, tumor location, total tumor volume, or SRS dose.

Clinical and Neuroimaging Follow-Up

The median follow-up time for all patients was 7.70 months. The median follow-up time for SNH patients was 5.93 months (IQR 2.53-15.09 months), and the median follow-up time for PH patients was 9.15 months (IQR 3.52-17.72 months) (p=0.09).

SNH patients had a significantly lower absolute number and monthly rate of neuroimaging studies after SRS (median 1.5 and 0.228, respectively) compared to PH patients (median 3 and 0.312, respectively) (p=0.008 and p=0.007, respectively) (**Table 2**). In contrast, SNH patients received a similar absolute number and monthly rate of clinical visits after SRS (median 1.5 and 0.298, respectively) compared to PH patients (median 2 and 0.288, respectively) (p=0.23 and p=0.97, respectively).

Incidence of Neurologic Symptoms and Salvage Treatments

SNH patients had significantly higher rates of any neurologic symptoms (33% SNH; 19% PH; p=0.05) and severe neurologic symptoms (15% SNH; 2% PH; p=0.003) following SRS (**Table 3**). SNH patients also had higher rates of hospitalization due to brain metastases (25% SNH; 7.5% PH; p=0.003) and salvage neurosurgery (17% SNH; 6% PH; p=0.04) following SRS. SNH patients did not experience significantly different rates of permanent neurologic symptoms, hospitalization for any reason, steroid requirement or dependency, salvage SRS, or salvage WBRT compared to PH patients.

Univariate Analysis

The median OS for all patients was 15.4 months. The median OS for SNH patients was 17.5 months and the median OS for PH patients was 15.1 months (p=0.34). SNH patients had higher risk of developing any neurologic symptoms (hazard ratio [HR], 2.64; 95% CI, 1.35-5.17; p=0.003), severe neurologic symptoms (HR, 9.20; 95% CI, 1.98-42.75; p<0.001), and permanent neurologic symptoms (HR, 2.33; 95% CI, 1.01-5.52; p=0.05). SNH patients were at higher risk for salvage neurosurgery following SRS (HR, 3.29; 95% CI, 1.19-9.08; p=0.01). SNH patients did not have higher risk for any hospitalization (HR, 1.00; 95% CI, 0.65-1.55; p=0.99) but did

have higher risk for hospitalization due to brain metastasis progression (HR, 3.64; 95% CI 1.40-9.44; p=0.005). There was no significant difference in risk of salvage SRS or salvage WBRT. Kaplan Meier survival curves for OS, salvage neurosurgery, any neurologic symptoms, and hospitalization for brain metastases are found in **Figure 1**.

Multivariable Analysis

On multivariable analysis, all-cause mortality was significantly associated with additional neuroimaging studies (HR, 0.65; 95% CI, 0.58-0.74; p<0.001), GPA (HR, 0.66; 95% CI, 0.46-0.94; p=0.02), breast histology (HR, 1.26; 95% CI 1.02-4.73; p=0.04), and melanoma histology (HR, 2.91; 95% CI, 1.36-6.22; p=0.006) (**Table 4**).

Significant risk factors for salvage neurosurgery included SNH setting (HR, 13.65; 95% CI, 3.31-56.29, p<0.001), neurologic symptoms at baseline (HR, 11.40; 95% CI, 2.82-46.12; p<0.001), number of brain metastases (HR, 1.26; 95% CI, 1.08-1.48; p=0.02), and melanoma histology (HR, 22.73; 95% CI, 3.24-159.29; p=0.002).

Significant risk factors for development of any neurologic symptoms included SNH setting (HR, 3.74; 95% CI, 1.60-8.74; p=0.002), early stage at diagnosis (HR, 0.28; 95% CI, 0.12-0.66; p=0.003), follow-up neuroimaging (HR, 0.87; 95% CI, 0.77-0.98; p=0.02), and breast histology (HR, 3.70; 95% CI, 1.30-10.52; p=0.01).

Significant risk factors for hospitalization due to brain metastasis progression included SNH setting (HR, 6.25; 95% CI, 2.22-17.57; p<0.001), follow-up clinical visits (HR, 0.75; 95% CI, 0.62-0.90; p=0.002), number of brain metastases (HR, 1.32; 95% CI, 1.05-1.65; p=0.02), and renal histology (HR, 4.58; 95% CI, 1.12-18.72; p=0.03).

Discussion

The goal of our study was to examine the effect of hospital setting and quality of follow-up on neurologic outcomes in brain metastasis patients treated with SRS alone. Although it is currently accepted that patients undergoing SRS alone require close clinical monitoring with neuroimaging due to the increased distant brain metastasis failure rate with omission of WBRT, we are not aware of any studies that have directly correlated follow-up clinical visits and neuroimaging studies with clinical outcomes. Furthermore, we did not find any studies that examined healthcare disparities in the brain metastasis population treated with SRS, and how

their treatment outcomes might depend on the clinical setting and patient demographics such as race, household income, or insurance status. Given the unique affiliation between the SNH and PH as teaching hospitals with collaboration for SRS treatment, we were especially well-positioned to carry out such a study.

We found that following SRS, SNH patients had higher incidence of and risk for any neurologic symptoms, severe neurologic symptoms, hospitalizations for brain metastases, and salvage neurosurgeries. Despite this, SNH and PH patients had similar OS. OS was high in both groups compared to historic survival after a diagnosis of brain metastases, which may be attributed to patient selection for SRS and improving systemic therapy.[17] The observation that SNH patients did not have worse median OS despite higher rates of neurologic symptoms and hospitalizations for brain metastases could be explained by excellent neurosurgical care allowing the successful salvage of patients with brain metastasis progression, as SNH patients also had higher rates of salvage neurosurgery. In addition, there may have been undetected differences in systemic disease burdens between the cohorts or our study may have been underpowered to detect differences in survival.

Although the two patient populations differed in terms of multiple baseline factors including younger age, more advanced stage at diagnosis of cancer, and longer time from diagnosis of brain metastases to SRS treatment for SNH patients, they had similar baseline KPS, GPA, histology, number of brain metastases, and total tumor volume. Studies have shown that the strongest predictors of outcomes following treatment of brain metastases with SRS include age, KPS, histology, number of brain metastases, and total tumor volume – all of which, besides age, were similar in the two groups.[18–22] Furthermore, the SNH patient population was significantly younger than the PH patient population, which typically confers better outcomes.

In multivariable analysis, SNH setting remained associated with increased risk for salvage neurosurgery, any neurologic symptoms, and hospitalization for brain metastases even after controlling for multiple other risk factors including tumor histology and time from initial consultation to SRS treatment. In an attempt to assess the quality of follow-up for patients after SRS, we recorded the number of routine follow-up clinical visits and neuroimaging studies that patients received. In comparison to PH patients, SNH patients received similar numbers of follow-up clinical visits but fewer neuroimaging studies.

On multivariable analysis, more follow-up clinical visits was correlated with fewer hospitalizations for brain metastases, while more follow-up neuroimaging studies was associated with better OS and less risk for development of any neurologic symptoms. These findings indicate that the poor outcomes observed in the SNH patient group were at least partly attributable to receiving less neuroimaging studies after SRS. We confirm and reemphasize the need for close clinical and neuroimaging surveillance after a treatment strategy of SRS alone for brain metastases. The comparatively smaller effect magnitude of clinical and neuroimaging follow-ups on these outcomes compared to SNH setting could potentially be due to challenges in quantifying the quality of follow-up, such as differentiating symptom-triggered visits from routine visits, accounting for differences in clinical follow-ups due to varying systemic therapy regimens, and determining whether patients received care at institutions outside our healthcare network.[23] Nonetheless, our results suggest that there may be other unaccounted for risk factors associated with a SNH practice setting, such as more patient comorbidities, less access to and compliance with systemic therapies, fewer hospital resources, and lower quality of medical care.[24–27]

There are numerous possible explanations for the disparity in number of neuroimaging follow-ups at the two hospitals, including differences in age, race, income, education, language, social supports, distance from treatment center, access to transportation, ability to take time off from work, and severity of disease.[24] The fact that SNH patients still received similar clinical follow-up implies that the underlying reason(s) are either specific to neuroimaging or affect compliance with neuroimaging studies more than clinical visits. An institution-specific barrier that we identified is the number of MRI scanners available. LAC+USC, which has 650 hospital beds, has three 1.5 Tesla MRI scanners whereas Keck Hospital, which has 471 hospital beds, has two 1.5 Tesla and three 3 Tesla MRI scanners (5 total) available for patient use. There is a general consensus among providers at our institutions that there are longer scheduling wait times for neuroimaging appointments at LAC+USC. Currently, LAC+USC has a >4 month backlog, defined as the time between the date the exam is ordered and the date of the neuroimaging appointment, whereas Keck Hospital has no backlog or waiting queue for scheduling neuroimaging appointments.

The finding that increasing number of brain metastases was associated with increased risk for salvage neurosurgery and hospitalization for brain metastases is consistent with other

analyses that found number of brain metastases to be a significant prognostic factor after treatment with SRS.[18–21] These studies focused on the effect of number of brain metastases on OS, but we now report that it may have prognostic significance for other neurologic outcomes such as salvage neurosurgery and hospitalization as well. Given that SNH and PH patients had similar numbers of brain metastases, this factor alone did not explain the difference in neurologic outcomes.

Limitations

The main limitations of our study are its retrospective nature, relatively small sample size, and heterogeneous cohorts. Patients at the PH and SNH had significantly different baseline characteristics that we attempted to account for in multivariable analysis. There were challenges in quantifying the quality of follow-up that may have lessened the true magnitude of effect on outcomes. Neurologic symptoms were determined retrospectively and thus were less reliable than a prospective study with real time data on neurologic status. Despite this, it is unlikely that the observed differences in neurologic outcomes between the hospitals can be accounted for merely by retrospective bias.

Conclusions

Brain metastasis patients followed in a SNH setting after treatment with SRS alone experienced higher rates of neurologic symptoms, severe neurologic symptoms, hospitalizations for brain metastases, and salvage neurosurgeries compared to PH patients. During follow-up, SNH patients received fewer neuroimaging studies. In multivariable analysis, early stage at diagnosis, more neuroimaging studies, and more clinical visits were protective for neurologic outcomes whereas SNH setting and higher number of brain metastases were risk factors for poor neurologic outcomes.

The treatment strategy of SRS alone with observation for brain metastases may be challenging to perform in the SNH setting due to fewer follow-up neuroimaging studies and other unidentified barriers associated with practice in a SNH setting. Patients and clinicians should consider patient access to follow-up care when deciding on the optimal strategy for treatment of brain metastases.

Suggestions for Future Work

Our study was conducted jointly at Norris, an academic medical center, and LAC+USC, one of the largest safety net hospitals in the United States, both located in Los Angeles, California. The results may or may not be generalizable to other practice settings where indigent patients are managed. Therefore, further study in this area at other indigent care settings is needed to confirm our findings. Additional studies are also needed to identify potential barriers to receiving appropriate brain metastasis follow-up care after SRS alone and potential interventions to improve compliance rates and neurologic outcomes in this setting. Our center plans to investigate the impact that a resident-led radiation oncology continuity clinic will have on patient compliance and outcomes after SRS alone.

Summary

In this retrospective cohort study of 153 patients with brain metastases, safety net hospital patients, as compared to private hospital patients, received fewer total follow-up neuroimaging studies (median 1.5 safety net vs. 3 private) and had higher rates of severe neurologic symptoms (15% safety net vs. 2% private), hospitalizations due to brain metastases (25% safety net vs. 7.5% private), and salvage neurosurgery (17% safety net vs. 6% private) following radiosurgery alone. Clinicians should consider practice setting and patient access to follow-up care when deciding on the optimal strategy for treatment of brain metastases.

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Table 1. Baseline Patient and Treatment Characteristics

	Private (n=93)	Safety Net (n=60)	All (n=153)	*p*-value
Age, median (IQR)	61 (53-69)	56 (46-63)	59 (50-66)	0.001
Sex				0.14
Male	50 (54%)	25 (42%)	75 (49%)	
Female	43 (46%)	35 (58%)	78 (51%)	
Race				<0.001
White non-Hispanic	54 (58%)	11 (18%)	65 (42%)	
Hispanic (any race)	15 (16%)	32 (53%)	47 (31%)	
Asian non-Hispanic	17 (18%)	7 (17%)	24 (16%)	
Black non-Hispanic or Other	7 (8%)	10 (12%)	17 (11%)	
Insurance status				<0.001
Private/managed care/Medicare	87 (94%)	8 (13%)	95 (62%)	
Medicaid, uninsured, or other	6 (6%)	52 (87%)	58 (38%)	
Household income, median (IQR)	72192 (50574-92960)	48754 (35693-60167)	59099 (43385-80864)	<0.001
KPS, median (IQR)	80 (75-90)	80 (80-90)	80 (80-90)	0.23
GPA, median (IQR)	1.5 (1-2)	1.75 (1-2.5)	1.5 (1-2.25)	0.67
Neurologically symptomatic at baseline	35 (38%)	23 (38%)	58 (38%)	0.93
Tumor histology				0.17
Lung adenocarcinoma	22 (24%)	21 (35%)	43 (28%)	
EGFR mutation	7 (35%)	4 (25%)	11 (31%)	0.52
ALK mutation	4 (20%)	3 (19%)	7 (19%)	0.93
Breast adenocarcinoma	11 (12%)	9 (15%)	20 (13%)	
Melanoma	16 (17%)	3 (5%)	19 (12%)	
BRAF mutation	6 (40%)	2 (67%)	8 (44%)	0.40
Renal cell carcinoma	13 (14%)	8 (13%)	21 (14%)	
Other	31 (33%)	19 (32%)	50 (33%)	
Stage at diagnosis				0.04
Stage 1-2	18 (22%)	5 (9%)	23 (16%)	
Stage 3-4	65 (78%)	52 (91%)	117 (84%)	

Table 1 Continued

	Private (n=93)	Safety Net (n=60)	All (n=153)	*p*-value
Brain metastases diagnosed within 3 months of primary	28 (30%)	27 (45%)	55	0.06
Prior surgical resection of brain metastases	41 (44%)	21 (35%)	62	0.26
Prior systemic therapy	87 (94%)	53 (88%)	140	0.26
Time from initial consultation to SRS, days, median (IQR)	9 (5-15)	24 (16.5-37)	15 (7-25)	<0.001
Time from brain metastases diagnosis to SRS, days, median (IQR)	22 (13.5-48.5)	43 (33-73.8)	33 (17-59)	<0.001
Number of brain metastases treated, median (IQR)	2 (1-3)	2 (1-4)	2 (1-3)	0.64
Total tumor volume, cc, median (IQR)	4.90 (1.33-10.07)	4.96 (1.61-9.79)	4.90 (1.46-9.93)	0.78
Total treatment volume, cc, median (IQR)	6.61 (1.84-13.76)	7.05 (2.68-13.82)	6.7 (2.10-13.73)	0.73
SRS dose, Gy, median (IQR)	20 (18-20)	20 (18-20)	20 (18-20)	0.73
Tumor location				0.19
Cerebral hemisphere	183 (76%)	132 (82%)	315 (79%)	
Cerebellum	40 (17%)	24 (15%)	64 (16%)	
Other	17 (7%)	5 (3%)	22 (5%)	

Abbreviations: IQR, interquartile range; KPS, Karnofsky Performance Status; GPA, graded prognostic assessment

Table 2. Clinical and Neuroimaging Follow-up

	Private (n=93)	**Safety Net (n=60)**	***p*-value**
Number of neuroimaging follow-ups, median (IQR)	3 (1-6)	1.5 (1-4)	0.008
Neuroimaging follow-ups per month, median (IQR)	0.312 (0.201-0.418)	0.228 (0.102-0.304)	0.007
Number of clinical follow-ups, median (IQR)	2 (1-5)	1.5 (1-3)	0.23
Clinical follow-ups per month, median (IQR)	0.288 (0.092-0.401)	0.298 (0.115-0.416)	0.97

Abbreviations: IQR, interquartile range

Table 3. Incidence of Neurologic Symptoms and Salvage Treatments

	Private (n=93)	**Safety Net (n=60)**	***p*-value**
Developed any neurologic symptoms	18 (19%)	20 (33%)	0.05
Developed severe neurologic symptoms	2 (2%)	9 (15%)	0.007
Permanent neurologic symptoms	10 (11%)	11 (18%)	0.18
Required steroids	33 (35%)	22 (37%)	0.88
Steroid dependency[a]	26 (28%)	17 (28%)	0.96
Hospitalization for any reason[b]	56 (60%)	33 (55%)	0.41
Hospitalization due to brain metastases	7 (7.5%)	15 (25%)	<0.001
Salvage neurosurgery	6 (6%)	10 (17%)	0.04
Salvage SRS	31 (33%)	15 (25%)	0.27
Salvage WBRT	19 (20%)	15 (25%)	0.51

[a]Defined as >2 weeks
[b]Other than scheduled chemotherapy or surgery admissions

Table 4. Multivariate Models with Significant Risk Factors

Risk Factor	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
	Overall Survival			
Additional neuroimaging follow-up	0.655 (0.583-0.737)	<0.001	0.653 (0.578-0.739)	<0.001
GPA	0.657 (0.481-0.896)	0.008	0.656 (0.460-0.935)	0.02
Additional day from consultation to SRS	1.003 (0.994-1.011)	0.52	0.999 (0.989, 1.009)	0.83
Tumor histology				
Lung adenocarcinoma	Ref.	Ref.	Ref.	Ref.
Breast adenocarcinoma	1.261 (0.599-2.652)	0.54	2.199 (1.023-4.726)	0.04
Melanoma	1.526 (0.725-3.211)	0.27	2.912 (1.363-6.224)	0.006
Renal cell carcinoma	1.256 (0.597-2.644)	0.55	1.545 (0.730-3.273)	0.26
Other	1.623 (0.887-2.972)	0.12	1.496 (0.808-2.773)	0.20
	Salvage Neurosurgery			
Safety net hospital	3.293 (1.194-9.082)	0.02	13.65 (3.311-56.29)	<0.001
Neurologic symptoms at baseline	3.313 (1.218-9.012)	0.02	11.40 (2.819-46.12)	<0.001
Additional brain metastasis	1.155 (1.002-1.332)	0.05	1.260 (1.074-1.478)	0.005
Additional day from consultation to SRS	1.001 (0.980,1.022)	0.96	0.994 (0.955-1.036)	0.79
Tumor histology				
Lung adenocarcinoma	Ref.	Ref.	Ref.	Ref.
Breast adenocarcinoma	1.023 (0.092-11.29)	0.99	0.493 (0.039-6.207)	0.58
Melanoma	7.082 (1.368-36.68)	0.02	22.73 (3.244-159.29)	0.002
Renal cell carcinoma	3.402 (0.567-20.41)	0.18	5.763 (0.907-36.64)	0.06
Other	3.537 (0.679-18.41)	0.13	4.250 (0.790-22.87)	0.09
	Any Neurologic Symptoms			
Safety net hospital	2.644 (1.352-5.172)	0.004	3.739 (1.599-8.743)	0.002
Early stage (1-2) at diagnosis	0.377 (0.183-0.774)	0.008	0.280 (0.120-0.656)	0.003
Additional neuroimaging follow-up	0.859 (0.759-0.972)	0.02	0.865 (0.766-0.977)	0.02
Additional day from consultation to SRS	0.997 (0.980-1.014)	0.70	0.979 (0.957-1.002)	0.08
Tumor histology				
Lung adenocarcinoma	Ref.	Ref.	Ref.	Ref.
Breast adenocarcinoma	3.103 (1.120-8.598)	0.03	3.702 (1.303-10.52)	0.01
Melanoma	2.162 (0.724-6.456)	0.17	2.851 (0.915-8.877)	0.07
Renal cell carcinoma	1.412 (0.446-4.468)	0.56	2.301 (0.720-7.360)	0.16
Other	1.922 (0.712-5.190)	0.20	1.470 (0.532-4.061)	0.46

Table 4 Continued

	Hospitalization for Brain Metastases			
Safety net hospital	4.371 (1.693-11.29)	0.002	6.248 (2.222-17.57)	<0.001
Additional clinical follow-up	0.786 (0.659-0.937)	0.007	0.749 (0.622-0.902)	0.002
Additional brain metastasis	1.216 (1.003-1.474)	0.46	1.316 (1.052-1.647)	0.02
Additional day from consultation to SRS	1.000 (0.984-1.017)	0.971	0.988 (0.958-1.018)	0.42
Tumor histology				
Lung adenocarcinoma	Ref.	Ref.	Ref.	Ref.
Breast adenocarcinoma	1.183 (0.283-4.959)	0.82	2.585 (0.576-11.60)	0.22
Melanoma	2.592 (0.689-9.746)	0.16	3.360 (0.875-12.90)	0.08
Renal cell carcinoma	2.948 (0.777-11.18)	0.11	4.584 (1.122-18.72)	0.03
Other	1.570 (0.450-5.471)	0.48	2.831 (0.727-11.02)	0.13

Abbreviations: HR, hazard ratio; CI, confidence interval; GPA, graded prognostic assessment

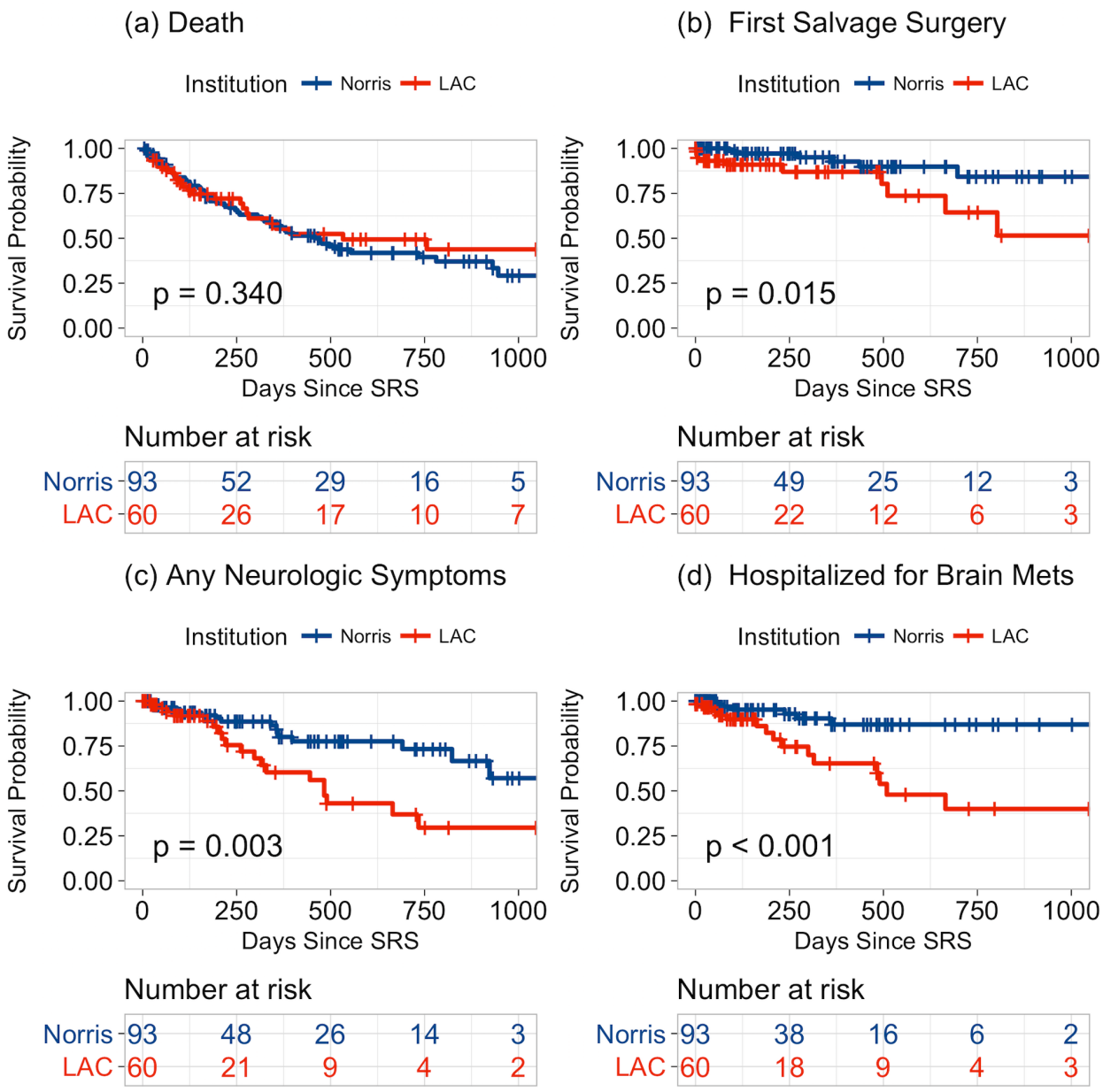

Figure 1: Kaplan Meier survival curves for (A) overall survival, (B) freedom from salvage neurosurgery, (C) freedom from any neurologic symptoms, and (D) freedom from hospitalization due to brain metastases stratified by hospital setting.